

Favorable outcome in non-Hodgkin lymphoma of the maxillary sinus treated with R-CHOP

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Submitted: 14 March 2012

Accepted: 5 July 2012

Arch Med Sci 2014; 10, 2: 406–409

DOI: 10.5114/aoms.2013.34986

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Non-Hodgkin lymphoma (NHL) accounts for less than 1% of all head and neck malignancies, although this anatomic location is the second most common extranodal site for NHL, lagging behind only the GI tract. Specifically, in the sinonasal tract, NHL is a common neoplasm, while its overall incidence ranges from 0.2% to 2% of all lymphoma cases in the Western world. Among paranasal sinuses, the maxillary sinus is the most common site of involvement, followed by the ethmoid, sphenoid and the frontal sinus. Men are predominantly affected and there is a prevalence of middle to older ages. The most common subtype is diffuse large B-cell lymphoma (DLBCL), comprising approximately two thirds of cases [1].

The clinical course of the disease is insidious, as there is either lack of symptoms or just vague, nonspecific symptoms unless the integrity of the sinus wall is breached and local signs of tumor infiltration develop. Symptoms related to tumor extension to nose, orbit or oral cavity include nasal discharge, nasal obstruction, proptosis, diplopia, trismus, headache, regional numbness and teeth loosening [2]. In this report, we present a case of DLBCL that developed in the maxillary sinus and presented as a non-tender swelling of the temporal region.

A 53-year-old woman presented to her dentist complaining of a non-tender tumefaction of the left temporal region and an intermittent mild toothache. She was afebrile and had neither excessive perspiration nor weight loss nor any other kind of systemic B symptoms. The patient mentioned that the swelling had been rapidly increasing within the last ten days, resulting in limited mouth opening. Her medical history was unremarkable except for well-controlled hypertension and knee osteoarthritis; her medications were anti-hypertensives and nonsteroidal anti-inflammatory drugs (NSAIDs). A periapical abscess was suspected, but dental examination, neck palpation, as well as panoramic X-ray failed to disclose any offending tooth or intraoral lesion. Therefore, she was referred for an ENT (ear, nose and throat) consultation. A diagnosis of atypical acute rhinosinusitis was entertained and she was started on a 2-week course of antibiotics. However, the patient did not improve and complained of worsening blurred vision in the left eye and diplopia. Exophthalmos, periorbital and facial edema became clinically apparent within the next 15 days. How-

ever, neither ophthalmoplegia nor other neurological deficits were noted and imaging studies with a head computed tomography (CT) scan and magnetic resonance imaging (MRI) were ordered.

A head MRI scan revealed a patulous, space-occupying lesion in the left sinus, extending into the left orbit and infratemporal fossa, pterygoid fossa and masseteric space. In addition, the lesion was abutting and displacing the inferolateral orbital muscles and was extended through the anterior sinus wall. The lesion showed soft tissue attenuation, and it was also eroding the posterior and superior sinus walls. The corresponding contrast-enhanced scan showed a moderate, slightly inhomogeneous enhancement of the mass (Figures 1 and 2). Enlargement of the regional cervical lymph nodes was also noted with bilateral distribution (Figure 3). This raised suspicion of a metastatic squamous cell carcinoma since this is the most commonly encountered malignancy of the maxillary sinus, although lymphoma was included in the differential diagnosis.

An incisional biopsy of both intramural (via a Caldwell-Luc access) and extramural lesions (through an intraoral incision) was then performed. Histological examination showed a diffusely infiltrating population of neoplastic lymphoid cells within a fibrotic stroma with vascular channels. Widespread deposition of lymphoid cells into the adjacent facial muscles and adipose tissue was also noted. The neoplastic cells were medium to large size and had oval to round vesicular nuclei, several with small nucleoli. There was a small to medium amount of amphophilic to pale eosinophilic cytoplasm and no obvious mitotic activity, apoptotic bodies or necrosis. Immunohistochemical staining revealed that CD20 was highly expressed, whereas CD10, CD5 and bcl-2 were only weakly expressed. Cells were negative for CD30, cyclin D1, MUM.1 and

bcl-6, pointing towards a diagnosis of diffuse large B-cell lymphoma subtype of NHL (DLBCL).

Staging CT as well as bone marrow biopsy did not reveal any further spread of the disease and the patient was staged as IIE. All blood counts and chemistries did not disclose any abnormalities, while lactate dehydrogenase (LDH) was well within the normal range. Overall, the International Prognostic Index (IPI) index was low. The patient received 8 cycles of the CHOP regimen (cyclophosphamide 650 mg/m², adriamycin 50 mg/m², vincristine 2 mg and dexamethasone 40 mg/day for 5 consecutive days each cycle) along with rituximab (anti-CD20, 375 mg/m²); chemotherapy was administered in 21-day cycles and was well tolerated. Imaging studies were negative at the end of the treatment while a positron emission tomography-computed tomography (PET-CT) scan performed at 1 month following the last chemotherapy session was negative for isotope uptake and the patient was considered to be in complete remission (Figures 4-5). Anti-CD20 was then administered every 2 months as a consolidation treatment for a total of 2 years.

In this report we present a case of maxillary sinus NHL of the DLBCL subtype that presented as a facial swelling along with signs of local infiltration and no systemic disease manifestations or distal site involvement. The initial diagnosis was rhinosinusitis although the rapid swelling and diplopia pointed towards a space-occupying lesion. Clinical suspicion for a developing tumor was documented with MRI scans and finally the histological diagnosis of DLBCL was attested by material obtained from an incisional biopsy.

Case reports and short series of sinus NHL have been reported in the literature although the sinuses are, overall, an uncommon site for NHL initial pres-

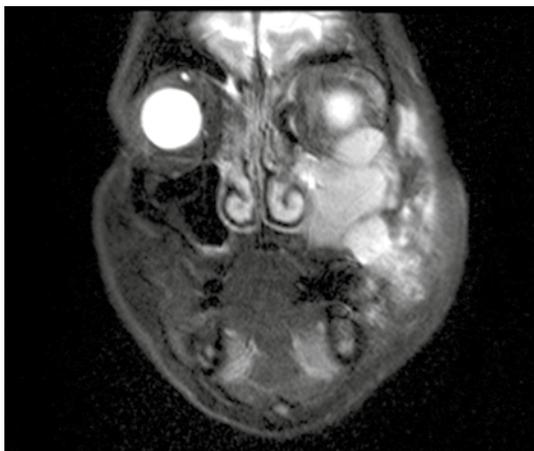


Figure 1. Coronal STIR MR image shows a soft tissue mass that occupies the left maxillary sinus. There is destruction of the medial and lateral walls, the floor of the left orbit and extension of the mass into the adjacent left buccinator and masseter muscle

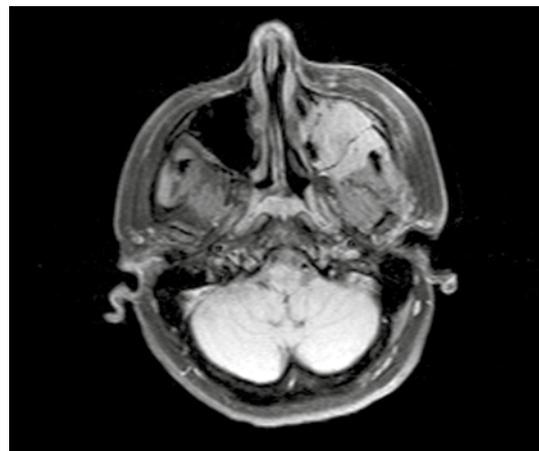


Figure 2. Axial T1-weighted contrast-enhanced fat suppressed MR image shows that the mass with strong enhancement also invades the posterior maxillary wall and extends posteriorly



Figure 3. Coronal T2-weighted MR image shows bilateral enlarged cervical lymph nodes

entation. In most of the published series, the disease manifests with local signs only and in the majority of the patients, the disease is limited to stage IE or IIE at diagnosis. Among the skull cavities, the maxillary sinus seems to be more often affected while the histological diagnosis of DLBCL seems to be the commonest in the Western world [2, 3]. However, in patients with HIV and in Asian and South American series, the common histological subtype seems to be NK/T cell NHL, which carries a far worse prognosis compared to DLBCL [2-5]. The reasons for the observed disparities are not currently apparent.

Treatment protocols for lymphomas of the sino-nasal tract consist of combination chemotherapy followed by involved field irradiation (IFRT) in eligible patients with good performance status. In a series of 14 patients, Complete remission (CR) was documented in 70% of patients treated with a CHOP regimen while overall survival (OS) reached 60% at 5 years [3]. In another cohort of patients



Figure 4 A, B. Positron emission tomography/computed tomography (PET/CT) for restaging post chemotherapy: transaxial PET shows no foci of abnormal tracer distribution and no evidence of recurrence in the corresponding CT image

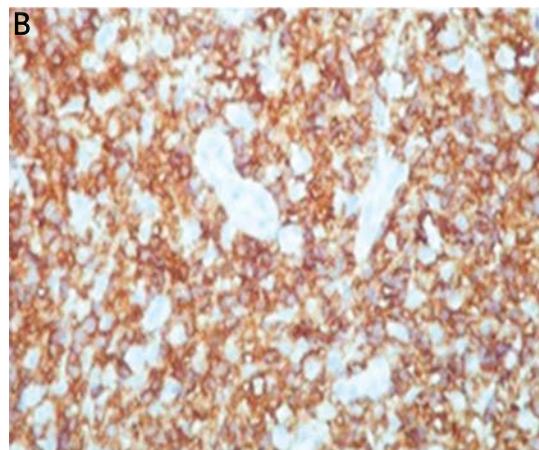
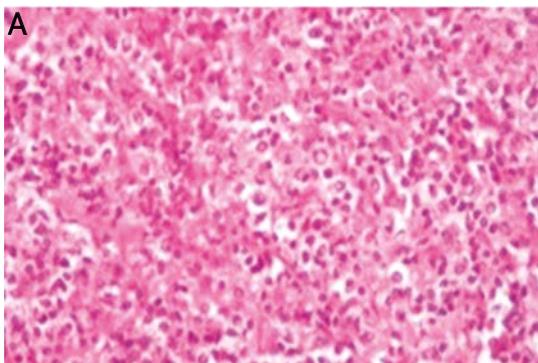


Figure 5. Histological images consistent with NHL

treated with chemotherapy plus radiation, a nearly 60% response rate was documented although the observation period was relatively short [2].

In the series with predominant DLBCL phenotype, the majority of the patients have been treated with combinations of chemotherapy plus RT with no randomization, making it impossible to draw any firm conclusions on the benefit of radiation. In our case, we decided to add anti-CD20 (rituximab) in the CHOP regimen since it has been documented that this monoclonal antibody improves CR rates in NHL patients while it seems to prolong overall survival when administered as maintenance therapy following eradication of the tumor [6]. However, in the case of aggressive sinus NHL, there is limited experience with anti-CD20 during maintenance or consolidation. In addition, the issue of maintenance in aggressive lymphomas treated with rituximab-containing regimens has not been settled yet [7]. There is also plausible evidence that radioimmunotherapy (RIT) is an effective treatment modality and increases CR, when used as consolidation treatment. A phase II trial of 90Y-ibritumomab tiuxetan consolidation following induction with R-CHOP in high-risk elderly patients with previously untreated DLBCL is in progress. Preliminary results have shown that consolidation has a favorable tolerability profile. Responses improved and OS and progression free survival (PFS) rates, after a median follow-up of 23 months, were at 88% and 80%, respectively. Two more trials are awaited in order to validate RIT efficacy [8]. Finally, better understanding of DLBCL genetic diversity and its ensuing refractoriness to current chemotherapy schemes may open new avenues in the individualization of treatment modalities, i.e. proteasome inhibitors and lenalidomide as single agents or in combination with chemotherapy [9].

Relapses of sinus lymphomas involve the affected area, the central nervous syndrome (CNS) or both; distant metastatic sites are far less common. Central nervous syndrome relapses occur in cases where invading lesions disrupt local barriers and expose the meninges to the developing lesion. Since such CNS relapses seem to occur often (4 of 7 relapsed patients in one series) [3], it seems reasonable that CNS prophylaxis should be administered in all the CHOP-treated patients since none of the medications used in the CHOP regimen crosses the blood-brain barrier (BBB). The addition of anti-CD20 does not protect the CNS in other types of NHL, making mandatory the prophylaxis of the CNS [10]. Whole brain irradiation or intrathecal chemotherapy has been utilized in order to obviate this outcome. Nevertheless, in our case, intrathecal chemotherapy was abandoned because of spinal canal stenosis. Instead, we replaced prednisolone with dexamethasone as the latter seems

to more efficiently cross the BBB. The decision to omit CNS prophylaxis was further supported by a negative FDG-PET scan which also confirmed CR in our patient. It has been established that interim fluorodeoxyglucose (18F)-PET (FDG-PET) scans have a strong positive predictive value when obtained after 2-3 chemotherapy cycles, allowing for a more aggressive treatment when a response is not achieved [11]. This observation was also validated in our case, with a lasting CR at 4 years following diagnosis, although PET/CT was performed at the end of induction.

Although rare, NHL should be included in the differential diagnosis of soft tissue tumors of the sinonasal tract, especially in patients in their 60s-70s. Obstructive symptoms are not always present and the prognosis is variable, depending on the stage and the aggressiveness of the tumor.

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